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EXAMINER	
BABIC, CHRISTOPHER M	
ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/598,140	PETRONIS ET AL.	
	Examiner	Art Unit	
	CHRISTOPHER M. BABIC	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,21 and 22* is/are rejected.

7)☒ Claim(s) *1-19,21 and 22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/24/07; 10/6/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of group I, claims 1-19, 21, and 22, in the reply filed on September 29, 2008 is acknowledged. Thus, the restriction requirement is still deemed proper and hereby made FINAL. As such, claim(s) 20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on pages 21 and 38. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

Claims 1-19, 21, and 22 are objected to because of the following informalities:

(a) The word "the" in step (b), line 1 of claim 1 should be deleted to provide for appropriate grammar.

(b) The words "analysing" (e.g. preamble) and "hybridising" (e.g. step f) and all variations thereof should be changed to "analyzing", "hybridizing" and all appropriate variations thereof to provide for appropriate grammar.

(c) There should be a space between the words "and" and "non-amplifiable" in step (d), line 3 of claim 10.

Appropriate correction is required.

Claim Rejections - 35 USC § 112 - Indefiniteness

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-4, 7-9, 17-19, and 21 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claim 2 recites the limitation "step j" in step (iii). There is insufficient antecedent basis for this limitation in the claim.

(b) Claim 3 recites the limitation "step1)" in line 1. There is insufficient antecedent basis for this limitation in the claim.

(c) Claim 4 recites the limitation "the CpG specific endonuclease" in line 1. There is insufficient antecedent basis for this limitation in the claim.

(d) Regarding claims 7, 17, and 21, the phrases "such as" and "for example" renders the claim indefinite because it is unclear whether the limitation(s) following the phrases are part of the claimed invention. See MPEP § 2173.05(d). For the application

of prior art, such limitation following the examples will be treated as exemplary and not necessarily required.

(e) Claims 8 and 18 recite the limitation "said probe" in line 1. There is insufficient antecedent basis for this limitation in the claim.

(f) Claims 9 and 19 recite the limitation "said fluorophore" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

1. Claims 10, 13, 14, and 16-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Yan et al. (J Nutr. 2002 Aug;132(8 Suppl):2430S-2434S).

Yan teaches methods of analyzing the methylation states of nucleotide sequences (fig. 2; 2431S-2433S, for example) comprising: a) selecting one or more genomic test nucleotide sequences from one or more subjects that exhibit a phenotype

of interest and one or more corresponding genomic control sequences from one or more control subjects that lack the phenotype of interest (fig. 2, genomic DNA sequences from cancer and non-cancer tissues, for example); b) digesting the genomic test nucleotide sequences and separately digesting the genomic control sequences with one or more frequent cutting restriction endonucleases (fig. 2, digestion with Mse1, a TTAA cutter, for example); c) ligating adaptor nucleotide sequences to the ends produced from step b) to produce ligated sequences (fig. 2, ligation to linkers, for example); d) cleaving the ligated sequences with one or more methylation-sensitive restriction endonucleases to produce amplifiable test nucleotide sequences, non-amplifiable test nucleotide sequences, amplifiable control nucleotides sequences and non-amplifiable control nucleotide sequences (fig. 2, methylation-sensitive digestion with BstU1, HpaII, etc. for example; e) amplifying the amplifiable test nucleotide sequences and amplifiable control nucleotide sequences to produce amplified test nucleotide sequences and amplified control nucleotide sequences (fig. 2, linker-PCR, for example); f) labeling the amplified test nucleotide sequences from step e) with a first label, and labeling the amplified control nucleotide sequence from step e) with a second label (fig. 2, Cy5 and Cy3 labeling, for example); g) hybridizing the labeled products of step f) with an array comprising a series of nucleotide sequences that are capable of hybridizing thereto (fig. 3, for example) ; and h) determining the ratio of the signals emitted by the first label relative to the second label for each set of hybridized nucleotide sequence on the array (fig. 3,4A, for example).

2. Claims 10, 13, 14, and 16-19 are rejected under 35 U.S.C. 102(e) as being anticipated by Huang (U.S. 6,605,432 B1).

Huang teaches methods of analyzing the methylation states of nucleotide sequences (fig. 2; col. 17-20, example 1, for example) comprising: a) selecting one or more genomic test nucleotide sequences from one or more subjects that exhibit a phenotype of interest and one or more corresponding genomic control sequences from one or more control subjects that lack the phenotype of interest (col. 18, genomic DNA sequences from cancer and non-cancer tissues, for example); b) digesting the genomic test nucleotide sequences and separately digesting the genomic control sequences with one or more frequent cutting restriction endonucleases (digestion with Mse1, a TTAA cutter, for example); c) ligating adaptor nucleotide sequences to the ends produced from step b) to produce ligated sequences (col. 18, ligation to linkers, for example); d) cleaving the ligated sequences with one or more methylation-sensitive restriction endonucleases to produce amplifiable test nucleotide sequences, non-amplifiable test nucleotide sequences, amplifiable control nucleotides sequences and non-amplifiable control nucleotide sequences (col. 18, methylation-sensitive digestion with BstUI, for example; e) amplifying the amplifiable test nucleotide sequences and amplifiable control nucleotide sequences to produce amplified test nucleotide sequences and amplified control nucleotide sequences (col. 18, PCR, for example); f) labeling the amplified test nucleotide sequences from step e) with a first label, and labeling the amplified control nucleotide sequence from step e) with a second label (col. 13, Cy5 and Cy3 labeling, for

example); g) hybridizing the labeled products of step f) with an array comprising a series of nucleotide sequences that are capable of hybridizing thereto (fig. 2, for example) ; and h) determining the ratio of the signals emitted by the first label relative to the second label for each set of hybridized nucleotide sequence on the array (fig. 2, , for example).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 1, 4-9, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yan et al. (J Nutr. 2002 Aug;132(8 Suppl):2430S-2434S) or Huang (U.S. 6,605,432 B1) in view of Chotai et al. (J Med Genet. 1998 Jun;35(6):472-5).

The teachings of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach the successive digestion of a nucleic sample with a methylation sensitive restriction enzyme followed by a methylation specific restriction enzyme.

With regard to claims 1, 5-9, and 22, Chotai provides a supportive disclosure that teaches the use of a methylation sensitive restriction enzyme (Not1) in conjunction with a methylation specific restriction enzyme (McrBC) to differentiate methylation status of target nucleic acids (abstract; fig. 1; pg. 473, SNRPN status, for example). It is clear from the teachings of the reference that the use of methylation sensitive restriction enzymes allow for the isolation or production of nucleic acid target sequences that contain collection of specific methylation sites, i.e. methylated CpG islands, as they are not digested due to the sensitivity of the restriction enzyme (e.g. Not1).

Returning to the teachings Yan and Huang, the methods clearly require intact methylated CpG islands or fragments, thus a skilled artisan would have been motivated to utilize restriction enzymes that produce such fragments.

Thus, in summary, it is submitted that it would have been *prima facie* obvious to a skilled artisan at the time of invention to utilize a methylation sensitive restriction

enzyme within the first digestion steps of the methods within Yan and Huang since the prior art demonstrates such enzymes as useful for producing intact methylated CpG island. It would have been further obvious to include a methylation insensitive enzyme to produce fragments between such methylated sites for further analysis.

With regard to claim 4, it is submitted that it would have been *prima facie* obvious to a skilled artisan at the time of invention to utilize McrBC within the second digestion steps of the methods within Yan and Huang since the prior art demonstrates such an enzymes as useful for digesting methylation specific nucleotide sites.

2. Claims 2 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yan et al. (J Nutr. 2002 Aug;132(8 Suppl):2430S-2434S) or Huang (U.S. 6,605,432 B1) in view of Chotai et al. (J Med Genet. 1998 Jun;35(6):472-5) as applied to claim 1 above, and in further view of Dean et al. (U.S. 6,617,137 B1).

The teachings of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach the amplification of target nucleic acid sequences prior to start of the methylation analysis methods.

Dean provides a supportive disclosure that teaches simplified methods of whole genome amplification for further biochemical analysis (abstract; col. 2-7, summary; col. 37, use of Phi29 DNA polymerase, for example). The reference further highlights that

the availability of an adequate quantity and quality of genomic DNA, which is frequently limiting in samples, is fundamental to genetic analysis (col. 1, for example).

Thus, in summary, it is submitted that it would have been *prima facie* obvious to a skilled artisan at the time of invention to utilize the Phi29 based genome amplification methods of Dean to amplify the disease and non-disease genomic DNA used within the methods of Yan and Huang, prior to the start of such methods, since the prior art demonstrates such a methods as useful for providing an adequate quantity and quality for genomic analysis.

3. Claims 11, 12, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yan et al. (J Nutr. 2002 Aug;132(8 Suppl):2430S-2434S) or Huang (U.S. 6,605,432 B1) in view of Dean et al. (U.S. 6,617,137 B1).

The teachings of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach the amplification of target nucleic acid sequences prior to start of the methylation analysis methods.

Dean provides a supportive disclosure that teaches simplified methods of whole genome amplification for further biochemical analysis (abstract; col. 2-7, summary; col. 37, use of Phi29 DNA polymerase, for example). The reference further highlights that the availability of an adequate quantity and quality of genomic DNA, which is frequently limiting in samples, is fundamental to genetic analysis (col. 1, for example).

Thus, in summary, it is submitted that it would have been *prima facie* obvious to a skilled artisan at the time of invention to utilize the Phi29 based genome amplification methods of Dean to amplify the disease and non-disease genomic DNA used within the methods of Yan and Huang, prior to the start of such methods, since the prior art demonstrates such a methods as useful for providing an adequate quantity and quality for genomic analysis.

4. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yan et al. (J Nutr. 2002 Aug;132(8 Suppl):2430S-2434S) or Huang (U.S. 6,605,432 B1) in view of Sutcliffe et al. (U.S. 6,110,680).

The teachings of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach the use of the claimed restriction enzymes.

Sutcliffe provides a supportive disclosure that demonstrates Csp61 as a frequent cutting restriction endonuclease (col. 18, for example).

Thus, in summary, it is submitted that it would have been *prima facie* obvious to a skilled artisan at the time of invention to utilize Csp61 in the methods of Yan and Huang since the prior art demonstrates such an enzyme as suitable for frequent cutting of a nucleic acid target.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 571-272-8507. The examiner can normally be reached on Monday-Friday 7:00AM to 4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christopher M. Babic/
Patent Examiner

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